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REVIEW

Bloodstream infections in the Intensive Care Unit

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ABSTRACT
Bloodstream infections (BSIs) represent a common complication among critically ill patients and a leading cause of morbidity and mortality. The prompt initiation of an effective antibiotic therapy is necessary in order to reduce mortality and to improve clinical outcomes. However, the choice of the empiric antibiotic regimen is often challenging, due to the worldwide spread of multi-drug resistant (MDR) organisms with reduced susceptibility to the available broad-spectrum antimicrobials. New therapeutic strategies are 5 to improve the effectiveness of antibiotic treatment while minimizing the risk of resistance selection.

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Introduction

Bloodstream infections (BSIs) are a frequent and life-threatening condition in hospital settings.[1-2] Critically ill patients are particularly predisposed to the acquisition of BSIs, which occur in approximately 7% of all patients within the first month of hospitalization in Intensive Care Unit (ICU).[3] The Extended Prevalence of Infection in the ICU Study (EPIC II) conducted in 2007 showed that in ICU approximately 15% of patients had a BSI on the day of the study.[4] In this context, BSIs are associated with particularly high mortality rates, ranging between 40% and 60%, with an overall 3-fold increase in the risk of hospital death.[3,5-6] The acquisition of a BSI also results in increased length of ICU-stay and healthcare-related costs.[7-8]

The prompt initiation of an effective antibiotic treatment has demonstrated to reduce mortality and improve clinical outcomes, particularly when severe sepsis or septic shock are present.[9-11] However, due to the widespread diffusion of multi-drug resistant (MDR) pathogens, the most commonly employed empiric regimens are often inappropriate, with an increased morbidity and mortality.[12-13]

In this article we will review the clinical and epidemiological characteristics of ICU-acquired BSIs (ICU-BSIs), with a specific focus on the problem of antimicrobial resistance and therapeutic strategies for empiric and targeted antibiotic therapy.

Epidemiology

ICU-BSIs present peculiar epidemiologic and microbiologic characteristics when compared with community-acquired- (CA) and hospital-acquired- (HA) BSIs.[1,14-15] Critically ill patients are subjected to a specific spectrum of risk factors, including high illness severity at admission (APACHE III score), prolonged stay, need for mechanical ventilation, renal replacement therapy, recent surgery, and immunosuppression.[2,5,16-18] The extensive use of intravascular catheters, however, is recognized as the most important factor contributing to the occurrence of BSI.[19-20] Central venous catheters, in particular, represent the intravascular devices that are most frequently associated with the acquisition of a BSI, although arterial catheters can be also involved.[2,5,21]

Catheter-related BSIs (CR-BSIs) (defined as the growth of the same pathogen from catheter tip and peripheral blood culture), which represent up to 30% of cases, and primary BSIs, accounting for around 35% of cases, are the most common types of BSI in ICU.[22-23] Ventilator-Associated-Pneumonia (VAP), which is a frequent complication when mechanical ventilation is required, is bacteraemic in around 15% of cases, and represent the most common source of secondary bacteraemia in critically ill patients.[23-25] Secondary BSIs, mainly originating from lower respiratory tract and abdominal infections (including infections developing from urinary tract), account for the majority of BSI cases acquired

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in the community or in the hospital requiring ICU admission.[16]

Microbiology

In a recent point-prevalence survey, *Magill et al* found that Gram-positive pathogens were the most frequently isolated pathogens in HA-BSIs, followed by *Candida* spp.[2]

In the specific subset of ICU-BSIs, Gram-positives (mainly *Staphylococcus aureus*), represent the most commonly isolated organisms.[3,6,23] Alarmingly, the isolation of *S. aureus* in blood cultures has been independently associated with increased mortality,[5] even if CR-BSIs, which are a frequent source when infection is sustained by *S. aureus*, are generally characterized by better clinical outcomes compared with other sources of BSI and primary bacteraemia.[3,5] VAP is also a common source of infection when BSIs are caused by *S. aureus*.[24-25]

Among Gram-negative pathogens, the most commonly isolates are *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumanii*, and *Pseudomonas aeruginosa*, typically isolated from abdominal or urinary tract sites.[4,26] CR- and primary BSIs can be occasionally caused by these pathogens.[3]

Candida spp plays also a major role in ICU, accounting for 8-15% of cases of BSIs,[5,27] with a prevalence of 6.9 per 1000 patients.[28] Moreover, patients with *Candida* BSIs had the greatest crude ICU mortality when compared with other organisms.[28]

Antibiotic resistance

During the last years, antimicrobial resistance has progressively increased worldwide, resulting in delays in the prescription of an effective antibiotic treatment and high mortality rates, non only in ICU setting.[29-30] Tumbarello *et al.* reported that nearly 50% of patients with a BSI sustained by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriacae* did not receive an adequate antibiotic treatment within 72 hours from blood cultures, leading to a 3-fold increase in mortality.[31] Similarly, in more than one third of BSIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA), empiric antibiotic treatment was found not effective, and the inadequacy of antibiotic regimen represented an independent risk factor for mortality.[32]

Methicillin-resistance in *S. aureus* is one of the most important issue encountered in clinical practice, involving 18% of the isolates in Europe in 2013, with a wide variability between different countries and resistance rates ranging from 0% to 64.5%.[33] Overall, higher rates of resistance have been reported in southern Europe (mainly Greece, Italy and Portugal), whereas in the Northern countries less than 1% of all isolates display resistance to methicillin.[33] In the ICU setting, in particular, the problem of MRSA prevalence is even more alarming. The most impressive data comes from the recent EUROBACT study, encompassing 1,156 patients admitted to ICU with a new diagnosis of HA-BSI and reporting methicillin-resistance rates in up to 50% of isolates.[26] For this reason, the prescription of vancomycin has progressively increased in recent years and still represents the most frequently used antimicrobial with activity against MRSA in critically ill patients.[26,34] Nevertheless, a continuous elevation of minimum-inhibitory concentrations (MICs) for vancomycin (known as the "*MIC-creep*" phenomenon) has been observed worldwide, although with a wide variability between different countries and institution.[35-36] The Centers for Disease Control (CDC) classified resistant bacteria as vancomycin-intermediate *S. aureus* (VISA) with MIC between 8 and 16 μg/mL, hetero-resistant VISA (h-VISA) with MIC between 1 and 4 μg/mL and vancomycin-resistant (VRSA) with MIC above 32 μg/mL. [37] As a result, the efficacy of vancomycin in MRSA bacteremia, which mainly depends on the MIC of the pathogen, has been questioned. In particular, MRSA bacteraemia treated with vancomycin has been associated with clinical failure and higher mortality if the strain displayed vancomycin MIC >1 mg/L.[38-40] Furthermore, vancomycin through concentrations $\geq$15 mg/L, necessary to overcome the higher MIC values, increases the risk of nephrotoxicity, which represents a frequent adverse event also when standard doses are used.[41]

Regarding Gram-negative organisms, the EUROBACT study found that MDR Gram-negative pathogens play a role in more than half of cases in ICU.[27] BSIs due to ESBL-producing *Enterobacteriacae* represent a challenge for clinicians, due to the resistance of the organisms to third generation cephalosporins. The effectiveness of antibiotic regimens including β-lactam/β-lactamase inhibitors has not been demonstrated in randomized clinical trials, in particular in the subset of critically ill patients, and carbapenems are often used as the first choice.[42] As a consequence, carbapenem-resistance rates have progressively increased, with *Acinetobacter* spp., *Klebsiella* spp and *Pseudomonas* spp. showing carbapenem resistance in 69%, 37% and 5.7% of cases, respectively, in patients with HA-BSIs managed in ICU in Europe.[27] However, carbapenem-resistance is widely jeopardized between different countries, with the higher reported rates in the southern European ICUs.[43] Few treatment options for carbapenem-resistant pathogens are available so far, and the use of combination regimens including colistin and/or tigecycline in association with a

carbapenem have been associated to a survival benefit when compared to a monotherapy in small observational studies.[44-45]. Unfortunately, MDR pathogens are often resistant to aminoglycosides, and cases of colistin resistance have been reported more and more frequently in areas where MDR Gram negatives are more common, with carbapenemase-producing *Klebsiella pneumonia* (KPC) showing colistin-resistance in up to 20% of isolates in Italian and Greek ICUs.[46-49]

Another emerging problem is fluconazole-resistance in *Candida* spp, which varies greatly by different countries and species, with the highest overall resistance rates reported in Denmark (33%) and the lowest in the Republic of Korea (0,9%).[50] In *Candida albicans*, which is responsible for the great majority of cases of candidaemia, resistance to fluconazole involves up to 5% of isolates worldwide, as reported by recent studies.[51-52]

Empiric therapy

In critically ill patients, a delay in the prescription of an adequate empiric antibiotic therapy may result in increased mortality, whereas the early prescription of an effective antimicrobial treatment is linked to improved clinical outcomes.[9-13] Also, the switch to an effective antimicrobial therapy upon availability of the susceptibility test is still associated with increased mortality compared with the prescription of an early effective regimen.[31]

For this reason, the empiric prescription of broad-spectrum antibiotics against the most likely involved pathogens, followed by de-escalation to a narrower spectrum therapy when patients' clinical conditions are stable and susceptibility tests are available, should be the most common and appropriate strategy. Nevertheless, due to the progressive increase in antimicrobial resistance, an empiric monotherapy with either piperacillin/tazobactam or a carbapenem can be inadequate in almost one third of cases in HA-BSIs managed in ICU.[27]

In order to provide an adequate empiric coverage, a thorough evaluation of the presence of risk factors for the acquisition of a BSI sustained by MDR pathogens is paramount. Specifically, the knowledge of the local epidemiology and resistance patterns are key, as a wide variability in resistance rates exists between different countries and institutions.[32,43] Moreover, the eventual previous colonization with MDR pathogens should be considered, since it significantly increases the risk of acquisition of an infection sustained by the same pathogen.[53-55] Risk factors for the acquisition of infections due to MDR bacteria are summarized in Table 1.[32,55-60]

Another important element in the management of critically ill patients is the optimization of antimicrobial doses and ways of administration in order to achieve and maintain optimal plasmatic concentrations, finding the balance between the pharmacokinetic characteristics of each antimicrobial and the pathophysiological modifications occurring during sepsis.[61] Suggested doses of the most common antimicrobials used in critically ill patients and administration schedules are reported in Table 2.[61-70]

Table 1. Risk factors for BSIs due to MDR pathogens.

Local outbreaks of MDR and local epidemiology (high risk if resistance is reported in > 20% of isolates)
Previous colonization with MDR pathogens
Exposure to broad-spectrum antimicrobial agents (in particular fluoroquinolones and/or third-generation cephalosporins and/or carbapenems) within 30 days
Admission to ICU
Mechanical ventilation
Devices placement (central venous catheter or other intravascular devices, urinary catheter)
Health-care associated or hospital-acquired infections
Recent surgery or invasive procedures within 30 days
Underlying severity of illness (Charlson index of ≥3)
Neutropenia (<500 PMN/mm^3)

Together with the prescription of antimicrobials, a prompt source control and the early removal of intravascular devices is mandatory, both in bacterial infections and candida infections.[40,71]

Providing an adequate empiric coverage, however, should not be the sole goal for the clinician, since the indiscriminate use of broad-spectrum antimicrobials is the main reason for the increasing selection of resistances.[72-73] In particular, carbapenem resistance is a major concern, as underlined by a recent study by Armand-Lefevre *et al.* showing that even a brief exposure to imipenem (1-3 days) can be a risk factor for introducing imipenem-resistant gram-negative pathogens carriage status.[74]

The vicious circle of overuse of broad spectrum antimicrobials and selection of resistances has made necessary the introduction of the concept of "antibiotic stewardship." The aim of antimicrobial stewardship is to optimize the use of antimicrobials by promoting the selection of the optimal antimicrobial regimen including dosing, duration of therapy and route of administration.[75]

Gram positive bacteria

Due to the "*MIC-creep*" phenomenon, alternatives to vancomycin should be considered in critically ill patients when bacteraemia is suspected, in particular when an empiric anti-MRSA regimen has to be initiated and an isolate with increased vancomycin MIC is suspected on the basis of local epidemiology. Daptomycin is a new lipopeptide characterized by a fast,

Table 2. suggested dosages of the most common antimicrobials used for the treatment of BSIs in critically ill patients.

Antimicrobial	Dose
Ceftazidime	15 mg/kg loading dose, then 6-8 g every 24 h c.i.
Cefepime	15 mg/kg loading dose, then 2 g every 8 h c.i.
Piperacillin/tazobactam	4.5 g (loading dose), then 18 g every 24 h c.i.
Meropenem	1-2 g every 8 h e.i.
Ertapenem	1 g every 12 h
Amikacin	25-30 mg/kg every 24 h
Gentamicin	7 mg/kg every 24 h
Vancomycin	1 g loading dose, then 30 mg/kg every 24 h c.i.
Daptomycin	8-10 mg/kg every 24 h
Tigecycline	100-200 mg (loading dose), then 50-100 mg every 12 h
Colistin	9 MU loading dose, 4.5 MU every 12 h
RifampinFosfomycin	600-900 mg every 24 h4-6 g every 6 h c.i.
Caspofungin	70 mg, then 50 mg every 24 h
Anidulafungin	200 mg, then 100 mg every 24 h
Micafungin	100 mg every 24 h

Notes. c.i.: continuous infusion
e.i: extended infusion (6-8 hours)

concentration-dependent bactericidal activity against the majority of Gram-positive bacteria, including MRSA, hVISA, VISA and VRSA.[76-77] Murray *et al.* compared daptomycin versus vancomycin for the treatment of bacteraemia sustained by MRSA with vancomycin MIC > 1 mg/L, and found that both 30-day mortality and persistent bacteraemia were significantly lower in patients treated with daptomycin.[39] Therefore, daptomycin is currently the first choice in MRSA bacteraemia with vancomycin MIC >1 mg/L. Moreover, an empiric antibiotic treatment with high-dose daptomycin (8-10 mg/kg/die) may be more effective than an adequate empiric regimen with glycopeptides or beta-lactams when a *S. aureus* BSI is suspected, especially in a contest of high local prevalence of MRSA.[78] Daptomycin is approved at a dose of 4 mg/kg for the treatment of complicated skin and soft-tissue infection (SSTI) and at 6 mg/kg for *S. aureus* BSIs, including treatment of right-sided endocarditis.[40] However, the optimal dosages for daptomycin have not been yet well established. Daptomycin standard doses (4-6 mg/kg/day) have been questioned in favor of higher ones (8-10 mg/kg/day), reported to provide higher clinical and microbiological cure rates through the maximization of the concentration-dependent bactericidal activity, overcoming the augmented renal clearance in septic patients and minimizing the selection of resistant strains.[79-80] Large randomized controlled trials evaluating high-dose daptomycin are lacking. Despite this, current guidelines suggest high-dose daptomycin for the treatment of infective endocarditis, based on expert opinion.[40] Daptomycin also possess a good anti-biofilm activity, representing a possible advantage when catheters or other devices are the source of infection.[81] Daptomycin is generally well tolerated and presents few side effects.[82-83]

Gram negative bacteria

The limited efficacy of available antimicrobial regimens is the major concern in the treatment of infections due to MDR Gram-negative pathogens, together with the lack of new effective antibiotic classes. In this setting, combination therapy approaches have been proposed in order to provide a better coverage including non-susceptible strains.[84] The prescription of a combination therapy has been advocated to be effective in reducing mortality in patients presenting with severe sepsis or septic shock,[85-86] and when the infection is sustained by *P. aeruginosa*,[87] but results are controversial.[88] The major advantages of combination regimens have been found in infections caused by MDR and, specifically, carbapenemase-producing organisms.[89-90]

For the treatment of BSIs sustained by KPC-producing *Enterobacteriacae*, which are the most common carbapenem-resistant nosocomial isolate, combination regimens including at least 2 active drugs have been associated with improved clinical outcomes and reduced mortality in comparison with the use of only one active drug, in particular when the combination includes a carbapenem.[45,91-92]

Tumbarello *et al.* analyzed a cohort of 125 patients with KPC-*K. pneumoniae*-BSIs and reported a significantly lower 30-day mortality in patients receiving a combination regimen compared with the ones treated with a monotherapy (34,1% vs 54,3%, P = 0,02). In particular, multivariate analysis found that a targeted therapy with meropenem in combination with colistin and tigecycline was independently associated with reduced mortality (OR:0.11; 95%CI: .02–.69; P = 0.01).[44] Otherwise, inadequate initial antibiotic treatment resulted an independent risk factor for increased mortality.[44] A recent study suggests that combination regimens including meropenem

might be more effective when the isolate has meropenem MIC $\leq$ 8 mg/L.[93] However, further evaluations are needed, in particular regarding the role of TDM, which may allow to achieve effective plasmatic concentrations also when meropenem MIC is > 8 mg/L.

For these reasons, a combination regimen including high-dose meropenem (1-2 g every 6-8 hours) together with high dose colistin (9 millions/daily) and/or high dose tigecycline (200 mg/daily) should be considered in critically ill patients, in particular when presenting with severe sepsis or septic shock and a carbapenem-resistant organism is suspected (i.e. previous colonization or infection due to a carbapenem-resistant strain, or when the risk of carbapenem-resistant pathogensis high on the basis of local epidemiology).

Candida

Patients with candidemia not receiving an adequate treatment within 12 hours after the collection of the blood cultures have been characterized as having an independent risk factor for increased mortality. Nevertheless, in only a minority of patients (less than 10%) the goal is achieved.[94] A major problem is represented by a low sensitivity of blood culture, ranging from 50% and 75%, and by the length of *Candida* growth *in vitro* (frequently more than a week). Thus, blood cultures are not considered the optimal early detection method for the diagnosis of candidaemia, although still representing the gold standard.[95] Both clinical scores based on the presence of well-defined risk factors for the development of invasive fungal infections and non-cultural biomarkers have been proposed in order to achieve an early diagnosis of candidaemia before the availability of blood cultures. Leon *et al.* proposed the "*Candida score*," which includes previous surgery, multifocal colonization, total parenteral nutrition and severe sepsis, and, for a cut-off value of 3, might be helpful for the identification of critically ill non-neutropenic septic patients at high risk for having a candidaemia.[96] However, into the wide clinical practice the "*Candida score*" have been associated with low sensitivity and specificity for the diagnosis of candidaemia, thus it should be used with caution.[97] The detection of (1-3)-β-D-glucan, which is a pan-fungal marker, represents a recent and useful tool for the rapid diagnosis of candidaemia in adult patients, with a cut-off value of 80 pg/mL. Serial determinations (twice a week) clinically-driven should be performed.[95] However, (1-3)-β-D-glucan does not represent a routine diagnostic method in standard practice so far, given that the test is available in only a minority of institutions. The use of procalcitonin (PCT) may also be useful when candidaemia is suspected, since, in a recent study by Martini *et al.*, a PCT cut-off value of 2 ng/mL separated *Candida* sepsis from bacterial sepsis with a sensitivity of 92%, a specificity of 93%, and positive and negative predictive values of 94% in critically ill surgical patients with signs of sepsis and at high risk for fungal infection, helping to rule out bacteraemia.[98] In order to achieve the goal of an early treatment of candidaemia, a pre-emptive antifungal therapy should be considered in critically ill patients with risk factors for candidaemia and positivity of (1-3)-β-D-glucan, when available.[99] Current European Society of Clinical Microbiology and Infectious Disease (ESCMID) guidelines recommend the use of echinocandins, due to their rapid fungicidal activity, the optimal anti-biofilm activity, the broader spectrum of activity, the lower resistance rates and the favorable safety profile, characterized by low toxicity and low drug-drug interactions compared with azoles.[99]

Targeted therapy

De-escalation therapy and optimization of therapy duration are strongly recommended by current guidelines and are part of the majority of the stewardship programs.[75,84] The main expected potential benefits are a reduction of antimicrobial resistance, lower antibiotic-related adverse events and overall decreased antimicrobial costs.[100]

De-escalation

Randomized controlled trials on de-escalation therapy in critically ill patients with BSIs are still lacking. However, 3 encouraging prospective observational studies supporting de-escalation have been recently published.[101-103] All these studies suggest that, in patients with severe sepsis or septic shock, de-escalation, defined as either the withdrawal of one or more antimicrobials or the switch to a narrower spectrum therapy after the availability of susceptibility tests, does not affect mortality, which is at least not worse in de-escalated patients than in not-de-escalated ones. Nevertheless, in critically ill septic patients the goal of de-escalation is achieved in only approximately 50% of cases, even when the cultural results are available.[102] The presence of many unsolved questions regarding de-escalation might be the reason for the decision of not to perform de-escalation into the wide clinical practice. In particular, the real effectiveness of de-escalation in reducing antimicrobial resistances have not been demonstrated so far, and studies specifically targeting severe infections sustained by MDR pathogens are lacking. Moreover, one study reported an increased number of superinfections and prolonged ICU-stay when de-escalation was performed.[103]

Table 3. Possible strategies for de-escalation in BSIs.

Pathogen	Antimicrobial options
MSSA or MSSE	Oxacillin (12-16 g every 24 h c.i.) or cefazolin (2-4 g every 8 h c.i)
Streptococci	Ampicillin (2 g every 4 h c.i.) or ceftriaxone (2 g every 24 h)
Enterococcus faecalis	Ampicillin (2 g every 4 h c.i.)
Non-ESBL *Enterobacteriacae*	Ceftriaxone (2 g every 24 h)
ESBL-*Enterobacteriacae*	Ertapenem (500 mg every 6 h, e.i. 4 h))
Susceptible *P.aeruginosa*	Piperacillin-tazobactam (4.5 g loading dose, then 18g q 24h c.i.) or antipseudomonal cephalosporin (ceftazidime 6 g every 24 h, c.i.or cefepime 6 g every 24 hours, c.i.)
Fluconazole-susceptible *Candida* spp	Fluconazole (loading dose 12 mg/kg every 12 h, then 400 mg every 24 h)

Notes. MSSA: methicillin-susceptible *Staphylococcus aureus*
MSSE: methicillin-susceptible *Staphylococcus epidermidis*

Nevertheless, in consideration of the available body of evidence showing that de-escalation do not affect mortality and the expected benefits on resistance selection and drug-related adverse events, de-escalation should be encouraged, when clinical setting allows it. Possible strategies for de-escalation in BSIs are listed in Table 3.

Duration of therapy

The optimal duration of therapy for BSIs in critically ill patients is poorly defined and randomized controlled trials examining duration of therapy in the specific setting of severely ill bacteraemic patients are not available. In general, recommended treatment duration should be between 7 and 14 days for bacteraemia related to central venous catheters, pneumonia, urinary tract, skin and soft tissue and intra-abdominal infections.[104] However, in recent years, groups of experts have suggested to keep antimicrobial therapy as short as possible, and the available body of evidence seems to support this concept.[105-106] In a recent meta-analysis Havey *et al.* found no significant differences in clinical cure, microbiologic cure, and survival among bacteraemic patients receiving shorter (5-7 days) vs. longer (7-21 days) duration of therapy, irrespective of the source of infection. The major limitation of this systematic review was the lack of studies specifically targeting bacteraemic patients and critically ill ones.[107] De Santis *et al.* in a retrospective study reported good clinical outcomes and low rates of clinical relapses in bacteraemic patients treated with short-course monotherapy (4-5 days) in ICU, in a clinical context characterized by the prevalence of Gram-positive pathogens [mainly coagulase-negative staphylococci (CoNS)] and low rates of MDR Gram-negative ones.[108] General consensus exists regarding a longer duration of therapy (14 days) for *S. aureus* bacteremia, in order to avoid the risk of relapse.[40] Moreover, in BSIs sustained by *Candida* spp. a duration of therapy of 14 days

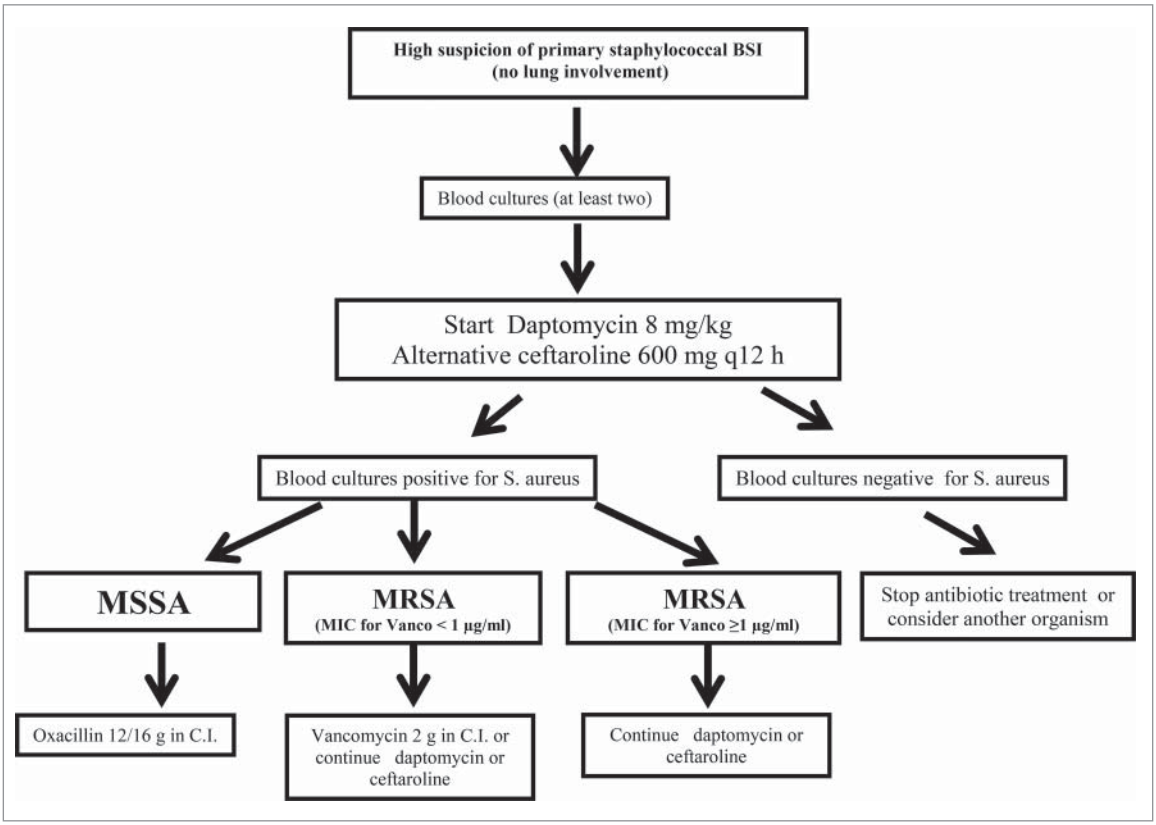

Figure 1. Treatment algorithm for empirical therapy of staphylococcal BSI

after the first negative blood culture is recommended by the guidelines.[99] Procalcitonin (PCT)-based approaches can contribute in reducing the duration of antimicrobial therapy in patients with severe sepsis and septic shock managed in ICU, as suggested in a recent meta-analysis by Prkno *et al.*[109] The authors analyzed 7 studies comprising a total of 1,075 patients with severe sepsis or septic shock and found that both hospital mortality and 28-day mortality were not different between PCT-guided therapy and standard treatment groups, whereas duration of antimicrobial therapy was significantly shorter when a PCT-guided therapy was applied. It is important to note that cut-off values of PCT levels to guide therapeutic decisions are not well established, varying between 0,25 ng/mL and 4 ng/mL in different studies and algorithms.[109] Thus, further investigations are needed.

Preventive strategies

Due to the high mortality and the frequent isolation of difficult-to treat pathogens, efforts should be made in order to prevent the development of BSI in critically ill patients.

The systematic use of isolation precautions, including standard measures (hand hygiene and gloves, gowns, eye protection use) and contact-based ones, represent a key strategy for reducing the transmission of the majority of bacteria and to control outbreaks of MDR pathogens.

Moreover, infection control programs based on culture surveillance from nasal and rectal swabs, together with appropriate isolation precautions, are effective in reducing the incidence of infections due to MDR pathogens, and should be encouraged in patients coming from highly endemic settings or with epidemiologic links to MDR cases.[110-112]

During the past years effective measures have been put in place in order to improve standardized protocols dictating catheter insertion and management in ICU, and a structured training for healthcare workers has been encouraged, leading to a significant reduction in the incidence of CR-BSIs in ICU.[113-116]

Conclusions

Several strategies should be implemented in order to improve the clinical outcome of BSIs in the ICU setting. The key point still remains a prompt initiation of an effective antibiotic treatment, which should be tailored in each single patient on the basis of the infection source, the most frequent pathogens isolated and the risk of antibiotic resistances. Increased attention, however, should be paid to strategies that can limit the progressive increase of antimicrobial resistance, through a careful use of available broad-spectrum antimicrobials and the improvement of surveillance and preventive measures. New antimicrobials with activity against MDR Gram-negative pathogens are urgently needed.

Abbreviations

BSIs	Bloodstream infections
ICU	Intensive Care Unit
MDR	Multidrug-resistant
ICU-BSIs	Intensive Care Unit-acquired bloodstream infections
CA	Community-acquired
HA	Hospital-acquired
CR-BSIs	Catheter-related bloodstream infections
VAP	Ventilator-associated pneumonia
ESBL	Extended-spectrum β-lactamase
MRSA	Methicillin-resistant *Staphylococcus aureus*
MICs	Minimum inhibitory concentrations
CDC	Centers for Disease Control
VISA	Vancomycin-intermediate *Staphylococcus aureus*
h-VISA	Heteroresistant vancomycin-intermediate *Staphylococcus aureus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
KPC	Carbapenemase-producing *Klebsiella pneumoniae*
SSTI	Skin and soft-tissue infection
CoNS	Coagulase-negative *Staphylococci*
PCT	Procalcitonin

Disclosure of potential conflicts of interest

MB received honoraria from Pfizer, Novartis, MSD, Gilead, Astellas, Bayer, Angelini, Tetraphase, Achaogen. The other authors declare no conflict of interest.

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